# Acute kidney injury after cardiac surgery

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# Chapter 6

## Postoperative renal dysfunction and preoperative left ventricular dysfunction predispose patients to increased long-term mortality after CABG surgery

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*Submitted*

# Abstract

**Background**: Preoperative left ventricular dysfunction and postoperative renal function deterioration are both associated with increased long-term mortality following cardiac surgery. The influence of preoperative left ventricular dysfunction on postoperative renal dysfunction and long term mortality is not defined.

**Methods:** We collected data from 641 consecutive patients undergoing coronary bypass surgery with cardiopulmonary bypass in 1991 at our institution. Prospective follow-up was through July 2004.

**Results**: In-hospital mortality was 2.7% (17 of 641). During follow-up 248 (40%) patients discharged alive died (5- and 10-years survival 90% and 70%, respectively). On univariate analysis preoperative left ventricular dysfunction (ejection fraction [EF] <50%) and an increase in serum creatinine ≥25% in the first postoperative week were associated with long-term mortality. The associated mortality risk was additive in predominantly non-overlapping patients groups: the hazard ratio (HR) for renal function deterioration only was 1.41 (95%CI 0.95-2.32, p=0.083; n=64), and for left ventricular dysfunction only 1.71 (95%CI 1.26-2.95, p=0.0026; n=73). In patients were both were present HR was 3.23 (95% CI 2.52-20.28, p<0.0001; n=20). Although post-operative renal dysfunction was associated with left ventricular dysfunction (p=0.008), both left ventricular dysfunction and postoperative renal function deterioration were independently associated with long-term mortality on multivariate analysis, as were age, preoperative estimated creatinine clearance and the use of venous conduits.

**Conclusions:** Postoperative renal function deterioration and preoperative left ventricular dysfunction both independently identify largely non-overlapping groups of patients with increased long-term mortality following coronary bypass surgery. In the group of patients with both factors present the mortality risks appear additive.

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# Introduction

Coronary artery bypass graft surgery (CABG) is the most frequently performed cardiac surgical procedure in the western world. Despite many advances in surgical, anesthetic, and postoperative intensive care procedures, CABG surgery continues to be associated with serious morbidity and mortality. Renal dysfunction is among the most serious complication after CABG affecting up to 30% of these patients.[1,2] Serious renal dysfunction requiring renal replacement therapy has a high mortality rate up to 80%.[3] In contrast, it is generally perceived that temporary worsening of renal function after cardiac surgery has little clinical relevance.[4] Recently, however several studies clearly demonstrated that small changes in renal function across a broad spectrum of medical and surgical conditions including cardiac and vascular surgery resulted in increased in-hospital morbidity and mortality,[5-7] and increased use of hospital resources. After cardiac surgery the in-hospital mortality associated with postoperative renal dysfunction ranged from 15 to 20% compared to 1.1% in patients without renal dysfunction.[3,5] Moreover, there is emerging evidence that temporary renal dysfunction also adversely affects long-term survival in medical and surgical patients.[6,7] In addition we recently demonstrated, in a cohort of cardiac surgical patients with a follow-up time of 100 months, that patients with postoperative renal dysfunction (>25% percent increase of serum creatinine from baseline) have higher long-term mortality rates.[3] Interestingly, the higher mortality rates were similar for all patients with postoperative renal dysfunction, whether the creatinine levels had returned to the preoperative baseline at discharge or not.

Postoperative renal dysfunction is caused by multiple factors. One of the main risk factors has been identified in a prospective cohort study, which demonstrated that the probability of developing acute renal failure after cardiac surgery mainly depends on poor preoperative cardiac performance.[8] In accordance, a later prospective follow up study of patients with preoperative left ventricular dysfunction undergoing isolated CABG surgery showed higher operative and postoperative 5-year mortality rates.[9] Nowadays an increasing number of patients scheduled to undergo CABG surgery has impaired left ventricular function.[9,10] The contribution of preoperative left ventricular dysfunction on postoperative renal dysfunction, with its associated increased long-term mortality, has to our knowledge not been studied in CABG patients.

In our previous cohort study we included all adult cardiac surgical patients after different type of operations. We found increased long term mortality in the group of patients who had postoperative renal function deterioration.[3] The present study group consists of all CABG patients from the earlier study cohort. We evaluated the contribution of preoperative left ventricular dysfunction to postoperative renal function deterioration. Moreover, we analyzed the combined influence of both conditions on long-term mortality. Furthermore, we hypothesized that the earlier observed increased mortality rate after postoperative renal dysfunction remains a permanent risk factor and therefore we extended the follow up period from 8 to 13.5 years for this patient category.

## Material and methods

Institutional approval was obtained and the need for informed consent was waived. All adult patients who underwent elective or emergency isolated coronary artery bypass surgery with cardiopulmonary bypass in 1991 entered the study. Patients on dialysis prior to cardiac surgery were excluded from further analysis (n=6). Included were 641 consecutive patients, and the data of patient charts, intensive care unit (ICU) charts, and anesthesia records of these patients were entered into a database. The following variables were assessed.

*Preoperative data*
Age, gender, body mass index (BMI), cerebral vascular disease, peripheral vascular disease, diabetes, hypertension, hypercholesterolemia, pulmonary disease (requiring chronic bronchodilator therapy), baseline serum creatinine (serum creatinine was obtained the day before surgery and in emergency cases just before surgery), congestive heart failure, previous myocardial infarction, previous cardiac operation, previous percutaneous angioplasty, number of diseased coronary arteries with stenosis > 70%, left main coronary artery stenosis > 50%, urgent and emergent surgical priority, and radiocontrast agent within 1wk were assesed. Preoperative left ventricular function was measured by left ventriculography in the right anterior oblique position as a routine registration in conjunction with preoperative coronary angiography and evaluated by the attending cardiologist; ventricular function was catagorized into three groups: normal left ventricular function: (ejection fraction >50%), moderate left ventricular function (ejection fraction >25% and <50%), and markedly reduced left ventricular function (ejection fraction <25%). In four patients preoperative left ventricular measurement was missing (0.6%). The Cockroft-Gault formula was used to estimate preoperative creatinine clearance.[11]

*Intraoperative data*
Coronary artery bypass surgery was done according to the institutional protocol. The left internal mammary artery has been used as the graft of choice to bypass the left anterior descending branch (LAD). The decision to use arterial or venous conduits was made by the attending surgeon. Arterial conduits include left and right internal mammary arteries (LIMA, RIMA) and the gastroepiploic artery (GEA). Saphenous veins were used as venous conduits. The use of arterial or venous conduits was divided into catagories: 1) complete arterial revascularization; 2) arterial and venous conduits; 3) venous conduits. Other intraoperative data include, use of aprotinin, duration of CPB, duration of operation, urine output during operation, and lowest hematocrit during CPB.

*Postoperative data*
Surgical re-exploration for bleeding or cardiac tamponade, myocardial infarction, serum creatinine at the first, second, seventh postoperative day, and at discharge from the hospital, cerebral stroke, intra aortic balloon pump (IABP), length of stay

in the intensive care unit, dialysis, low cardiac output syndrome (cardiac index $<2.2$ L/min/m$^2$), in-hospital mortality were registered. Postoperative renal function deterioration was defined as an increase in the serum creatinine level in the first postoperative week of at least 25 % from the preoperative level.

*Long-term follow-up data*

After a follow-up time of 13.5 years the vital status of all patients as of July 2004 was ascertained by extracting data from the patient charts of the outpatient clinic or by contacting the general practitioner of the patient. If a patient had died during follow-up, the date of death was established. No patients were lost and outcome assessment was complete.

*Anesthesia, CPB and ICU management*

The patients received total intravenous anesthesia. Induction started with sufentanil (0.5 μg/ kg), midazolam (0.05-0.1 mg/kg), and pancuronium (0,1mg/kg) to facilitate tracheal intubation. Anesthesia was maintained with sufentanil (2 -5 μg/ kg) and a continuous infusion of midazolam (0.1 mg/kg/h). The patients lungs were ventilated with air and oxygen (FiO2=0.4). Radial artery and central venous pressures were continuously monitored. Aprotinin (2.000.000 IE) was given at the start of CPB at the discretion of the surgeon. Non-pulsatile CPB was performed with a non-occlusive roller pump and membrane oxygenator (Cobe Optima; Cobe Laboratories; Lakewood, CO). The extracorporeal circuit was primed with 500 ml of 6% hydroxyethyl starch and 1000 ml lactated Ringer's solution. An initial dose of heparin 300 IU/ kg was given before cannulation of the aorta and right atrium to obtain a kaolin-activated clotting time >400 s. Additional heparin was given during CPB when the kaolin-activated clotting time was less than 400 s. Flow during CPB was maintained at 2.2 L.min/m$^2$ during moderate hypothermia (320 C) with α-stat pH management. Cold St. Thomas solution was infused into the aortic root for cardioplegia during aortic cross-clamping. During CPB, the mean arterial pressure was kept between 60 and 90 mm Hg using phenylephrine or nitroglycerin as needed. After weaning of CPB protamine was given in a dose equal to the initial dose of heparin.

In the intensive care unit patients were managed according to a set protocol targeted at a cardiac index ≥2.2 l/min/m$^2$ and a urine production of ≥1 ml/kg/hour. Indications for initiation of renal replacement therapy were: signs and symptoms of extra cellular volume overload, azotemia, hyperkalemia, and metabolic acidosis that could not be managed with other therapies.

*Statistical analysis*

All statistical analysis were conducted using SPSS 11.0 for Windows. Data are given as mean ± SD.

Univariate testing of variables between the group of patients who died during hospitalization and the group of patients discharged alive was performed with the t-test for continuous variables and the $\chi^2$ test for discrete variables. Baseline variables were compared among the group with and without preoperative left ventricular

dysfunction. Multivariate analysis was performed to test the association of left ventricular function with different preoperative variables. Univariate testing was also performed to compare the group with and without postoperative renal function deterioration. We then used backward logistic multivariate analysis was to test the independent association of postoperative renal function deterioration with different variables. Variables with a $p < 0.1$ in the univariate analysis were included in the multivariate analysis.
In the patients who were discharged alive, long-term outcome was studied with Kaplan-Meier survival analysis, and the log rank test was used to compare survival between groups and hazard ratios (HR) and 95% confidence intervals (CI) were estimated for long-term mortality. For univariate survival analysis continuous variables were grouped according to quartiles. All variables with a p value < 0.1 in the univariate log rank test were included in a multivariate Cox regression analysis. Backward variable selection was used until only significant covariates remained in the model. Hazards ratios and 95% confidence intervals (95% CI) were estimated for independent risk factors. Statistical significance was accepted at $p< 0.05$.

## Results

Clinical characteristics, operative and postoperative variables of the cohort (n=641) are summarized in table 1, and dichotomized into patients that were discharged alive or died in hospital. The patients with markedly reduced left ventricular function (n=10) and moderate reduction in left ventricular function (n=90) were grouped together as left ventricular dysfunction. The in-hospital mortality in the entire cohort of coronary artery surgery patients was 2.7%. On univariate analysis the patients who died in the hospital were older than the patients discharged alive. Furthermore, the patients who died in the hospital had significantly more co morbid conditions, including lower estimated creatinine clearance, left ventricular dysfunction, pulmonary disease, and peripheral vascular disease, and use of aprotinin. They also had more serious operative complications, including longer duration of cardiopulmonary bypass, postoperative renal function deterioration, postoperative low output syndrome, and re-exploration. Renal replacement during hospital stay was required in 3 patients (0.5%) in the postoperative renal function deterioration group. Only one of these patients survived (67% mortality). In addition, we analyzed whether the intraoperative use of aprotinin was associated with adverse renal and cardiac effects. There was a trend towards a higher postoperative serum creatinine with a rise of 24 ±87% in the aprotinin group compared to 10±32% in the group without aprotinin (p=0.09). Moreover, in the aprotinin group significantly more patients had a postoperative myocardial infarction (7 versus 11 patients; p=0.022).
The patients with preoperative left ventricular dysfunction had lower estimated creatinine clearances (67,2 ml/min ±18,1 versus 74,4 ml/min ± 22.2; p=0.001), and a higher prevalence of peripheral vascular disease, prior percutaneous angioplasty, prior myocardial infarction, and triple vessel disease compared with good left

**Table 1.** Preoperative, intraoperative, and postoperative characteristics of 641 patients who underwent isolated coronary artery bypass grafting[a].

| | discharged alive | died in hospital | p value |
|---|---|---|---|
| No. of patients | 624 | 17 | |
| Age (yrs) | 63.2±9.2 | 67.6±7.7 | 0.03 |
| Male/female | 478/146 | 15/2 | 0.26 |
| BMI (kg/m2) | 25.0±2.9 | 25.2±3.0 | 0.31 |
| Preoperative Cr (μmol/l) | 100.1±21.9 | 112.3±25.7 | 0.07 |
| Cockroft-Gault clearance (ml/min) | 73.6±21.8 | 61.3.±14.9 | 0.004 |
| Preoperative left ventricular dysfunction (%) | 93 (14.9) | 7(41.2) | 0.003 |
| Triple vessel disease (%) | 363 (58.2) | 13(76.5) | 0.14 |
| Pulmonary disease (%) | 31(5.0) | 4(23.5) | 0.001 |
| Diabetes mellitus (%) | 72 (11.5) | 4(23.5) | 0.13 |
| Hypertension (%) | 157 (25.3) | 4(23.5) | 0.87 |
| Peripheral vascular disease (%) | 77 (12.4) | 6(35.3) | 0.005 |
| Prior myocardial infarction (%) | 304 (48.9) | 11(64.7) | 0.19 |
| Urgent and emergent surgical priority (%) | 59 (9.5) | 4(23.5) | 0.06 |
| Venous conduits only (%) | 64 (10.3) | 2 (11.7) | 0.84 |
| Aprotinin (%) | 110 (17.6 ) | 7 (41.2 ) | 0.013 |
| Duration of CPB (min) | 86.4±29.6 | 128.5±70.2 | 0.03 |
| Highest Postop Cr (μmol/l) | 110.2±43.2 | 223.6±151.5 | 0.007 |
| Cr change (%) | -4.0±16.0 | 30.9±51.0 | 0.012 |
| Renal function deterioration (%) | 84 (13.5) | 12 (70.6) | <0.001 |
| Re-exploration (%) | 22 (3.5) | 5(29.4) | <0.001 |
| Prior CABG (%) | 33 (5.3) | 2 (11.7) | 0.25 |
| Postoperative IABP (%) | 12 (1.9) | 1 (5.8) | 0.25 |
| Postoperative low output syndrome (%) | 18 (2.8) | 2 (11.7) | 0.04 |

[a] Data are mean ± SD.
BMI, body mass index; preoperative Cr, preoperative serum creatinine; CPB, cardiopulmonary bypass; Cr, serum creatinine; CABG, coronary artery bypass grafting; IABP, intraaortic balloon pump.

**Table 2.** Variables associated with preoperative left ventricular dysfunction by multiple logistic regression analysis[a].

| Variable | HR (95% CI) | p Value |
|---|---|---|
| Estimated creatinine clearance (ml/min) | 0.988(0.976-1.000) | 0.042 |
| Peripheral vascular disease | 2.39(1.35-4.24) | 0.003 |
| Prior myocardial infarction | 4.91(2.83-8.51) | <0.001 |
| Triple vessel disease | 2.30(1.34-3.97) | 0.003 |

[a] HR, hazards ratio; CI, confidence interval

**Table 3.** Predictive factors in multiple logistic regression analysis associated with postoperative renal function deterioration after coronary artery bypass surgerya.

| Variable | HR (95% CI) | P Value |
|---|---|---|
| Age (yr) | 1.034 (1.007-1.062) | 0.014 |
| Preoperative left ventricular dysfunction | 2.12 (1.22-3.67) | 0.008 |
| Re-exploration | 5.42 (2.30-12.77) | <0.001 |
| Emergency operation | 2.78 (1.47-5.22) | 0.002 |
| Postoperative IABP | 4.95 (1.49-16.40) | 0.013 |

[a] HR, hazards ratio; CI, confidence interval; IABP, intra-aortic balloon pump

ventricular function. Using multiple logistic regression an association of preoperative left ventricular dysfunction with preoperative estimated creatinine clearance, peripheral vascular disease, prior myocardial infarction, and triple vessel disease was found (Table 2).

Likewise, the independent association of postoperative renal function deterioration with different variables was tested using multivariate logistic regression analysis. Independent predictive factors for postoperative renal function deterioration were preoperatively related, age and left ventricular dysfunction and procedure related including, postoperative IABP, re-exploration, and emergency operation (Table 3).

During long-term follow-up 248 of the 624 patients discharged alive died (40%). Univariate analysis of long-term outcome in the patients discharged alive was analyzed with the logrank test (Table 4) and Kaplan-Meier survival analysis. Preoperative left ventricular dysfunction resulted in an increased long-term mortality with a HR of 1.88 (95%CI 1.52-3.22, $p<0.0001$) (figure 1). Long-term mortality was also seriously affected by postoperative renal function deterioration with an increased long-term mortality (HR 1.63; 95%CI 1.23-2.66, $p=0.0025$) (Figure 2). As preoperative left ventricular dysfunction was strongly associated with occurrence of postoperative renal dysfunction, and both were associated with long-term survival, we analyzed their combined influence on long-term survival (Figure 3). Postoperative renal function deterioration in the patients with a good ventricular function (n=64) resulted in a mortality risk with a HR of 1.41 (95%CI 0.95-2.32, $p=0.083$). The group of patients

**Table 4.** Risk factors associated with mortality during long-term follow-up in patients (n=614) discharged alive following coronary artery bypass surgery[a] (logrank test).

| Variable | HR (95% CI) | p value |
|---|---|---|
| Age (yr) < 57 | | |
| 57-64 | 2.68(1.60-3.92) | p<0.0001 |
| 65-70 | 3.55(2.10-4.83) | p<0.0001 |
| >70 | 7.09(4.26-8.90) | p<0.0001 |
| Preoperative Cr (μmol/l) >86 | | |
| 87-98 | 1.30(0.90-1.88) | p=0.16 |
| 99-110 | 1.16(0.79-1.71) | p=0.44 |
| >111 | 2.00(1.42-2.86) | p<0.0001 |
| Estimated creatinine clearance (ml/min) >84.7 | | |
| 71.8-84.7 | 2.18(1.37-3.35) | p=0.0009 |
| 57.8-71.7 | 3.73(2.36-5.17) | p<0.0001 |
| <57.7 | 5.10(3.26-6.81) | p<0.0001 |
| Peripheral vascular disease | 1.48(1.06-2.09) | p=0.023 |
| Prior myocardial infarction | 1.42(1.10-1.82) | P=0.006 |
| Triple vessel disease | 1.62(1.23-2.04) | p=0.0004 |
| Left ventricular dysfunction | 1.88(1.52-3.22) | p<0.0001 |
| Postoperative renal function deterioration | 1.63(1.23-2.66) | P=0.0025 |
| Venous conduits | 2.27(2.02-5.02) | P=0.0214 |

[a] HR, hazards ratio; CI, confidence interval; Cr, serum creatinine.

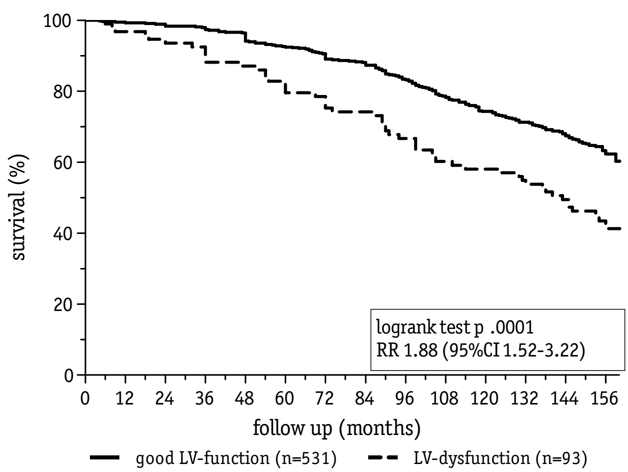


**Figure 1.** Preoperative left ventricular function and long-term postoperative survival.

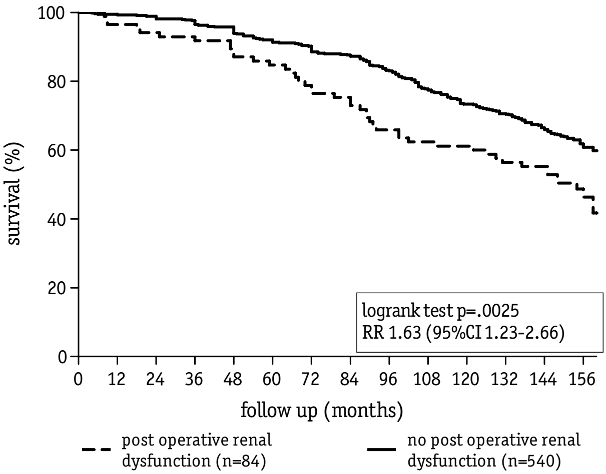


**Figure 2.** Long-term patient survival according to postoperative renal dysfunction.

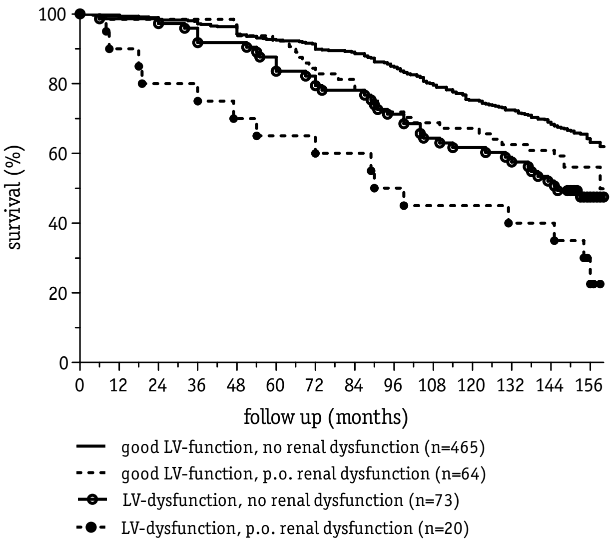


**Figure 3.** Long-term survival according to preoperative left ventricular function and occurence of postoperative renal dysfunction.

(n=73) with preoperative left ventricular dysfunction and no postoperative renal function deterioration showed a significant increased mortality risk with a HR of 1.71 (95%CI 1.26-2.95; p=0.0026). The highest mortality rate was observed in the group of patients (n=20) with a combination of preoperative left ventricular dysfunction and postoperative renal function deterioration (HR of 3.23; 95% CI 2.52-20.28, p<0.0001). During long-term follow-up none of the patients required dialysis for end-stage renal disease.

Table 5. Independent predictive factors in Cox proportional hazards analysis for long term mortality after coronary artery bypass surgery.

| Variable | HR (95% CI) | P Value |
|---|---|---|
| Age (yr) | 1.06 (1.04-1.09) | <0.001 |
| Left ventricular dysfunction | 1.62 (1.19-2.22) | 0.002 |
| Estimated creatinine clearance | 0.98 (0.97-0.99) | 0.004 |
| Venous conduits only | 1.40 (1.03-1.92) | 0.034 |
| Postoperative renal function deterioration | 1.42 (1.02-1.99) | 0.040 |

Univariate analysis clearly demonstrated an increased long-term mortality rate of preoperative left ventricular dysfunction and postoperative renal dysfunction. To study the influence of confounding variables we performed multivariate analysis. Variables associated with long-term outcome with a $p<0.1$ by univariate analysis were included in a multivariate Cox proportional hazards analysis to test the independent association with long-term outcome. In addition to the variables presented in table 4, congestive heart failure, perfusion time, and low cardiac output syndrome were included in the multivariate analysis. After adjusting for confounding variables preoperative left ventricular dysfunction and postoperative renal function deterioration remained significant predictor for long-term mortality. In addition age, estimated preoperative creatinine clearance, and the use of venous conduits were also independent risk factors for long-term mortality (Table 5)

## Discussion

The main finding of this study is that preoperative left ventricular dysfunction and the occurrence of immediate postoperative renal dysfunction, defined as >25% percent increase of serum creatinine from baseline, both independently identify groups of patients with increased long-term mortality following CABG surgery. Importantly, in the group of patients with both risk factors the long-term risk of mortality was additive, and nearly doubled. Furthermore, the continued follow-up of our study group clearly showed that the increased mortality risk of postoperative renal dysfunction still persisted after 13.5 year.
The observed in-hospital mortality rate of 2.7% in this cohort is consistent with published data.[8,12] Likewise, short-term mortality rates were increased in patients with preoperative left ventricular dysfunction and postoperative renal dysfunction.[5,9] Long-term survival rate in our patients was high, with an estimated 5-year survival of 90% in all the patients. Similar results were reported in the European Coronary Surgery Study with a follow-up time of 12 years.[13]

*Adverse effect of postoperative renal dysfunction on short-term mortality.*
The influence of renal dysfunction on increased in-hospital mortality has been studied in different patient categories including, medical- and cardiovascular surgical patients.[6,14] Chertow et al. [6] studied a large cohort of hospitalized patients with a wide variety of conditions, which were categorized according to the International Classification of Diseases (ICD9). They concluded that modest changes (>0.5mg/dl) in serum creatinine were clearly associated with mortality, length of stay and costs, even after adjustment for age, gender, admission diagnosis, severity of illness, and chronic kidney disease. Levy et al. evaluated the impact of contrast media induced renal dysfunction on mortality in a matched-pairs cohort study.[15] In-hospital mortality was increased in patients who developed renal dysfunction (defined as an increase in serum creatinine level of at least 25%) after radiocontrast procedures. Accordingly, Lassnigg et al. found that even a minimal increase of serum creatinine in patients after cardiothoracic surgery was associated with a substantial decrease in survival.[14] Also, after open abdominal aortic surgery small temporary changes in renal function, resulted in increased in-hospital mortality.[7] Thus, worsening of renal function in specific patient categories results in increased short- term mortality.

*Adverse effect of postoperative renal dysfunction on long-term mortality*
Until now, the importance of postoperative worsening of renal function on long-term survival has been ignored. In a recent study, patients after CABG surgery were stratified by the percentage increase in creatinine from baseline. After a follow-up of 90 days, patients with the largest creatinine increases (50% - 99% or >100%) had a significantly higher mortality compared with patients with a smaller increase (<50%).[16] Due to a limited follow-up time the survival in the categories was mainly determined by the mortality within 30 days, which is consistent with our reported in-hospital mortality. In addition to our previous observations,[3] the findings of the present study, with an extended follow-up period of 13.5 year, clearly confirm that modest changes of renal function in CABG patients result in an important effect on long-term mortality. Interestingly, Welten et al. described the same effect in a different group of patients after a 10-year follow-up.[7] Temporary worsening of renal function (>10% estimated creatinine clearance by Cockcroft-Gault formula) during the first three days following elective open abdominal aortic aneurysm surgery was associated with higher long-term mortality. Remarkably, although renal function may recover completely during the first postoperative week after this type of surgery, these patients remain at high risk of long-term mortality. We observed the same phenomenon: cardiac surgical patients with postoperative renal dysfunction have the same mortality risk whether the creatinine levels had returned to the preoperative baseline at discharge or not.[3] Thus, these findings suggest that temporary worsening of renal function after major cardio- and vascular surgery has an extended effect on long-term mortality.

*Adverse effect of Left ventricular dysfunction on mortality.*
In this study preoperative left ventricular dysfunction is a major risk factor for post-operative renal dysfunction and mortality. We analyzed the contribution of patient

and procedure related factors. In line with earlier studies[9,10] we observed an increased prevalence of peripheral vascular disease, previous myocardial infarction, and multi-vessel disease, and lower levels of estimated preoperative creatinine clearance in the patients with ventricular dysfunction. Preoperative left ventricular dysfunction may reduce the ability to cope with the stress of complicated surgery and hemodynamic derangements. Furthermore, these complications, including postoperative low cardiac output syndrome, re-exploration, and postoperative IABP, have impact on the perioperative hemodynamic stability and may have contributed to postoperative renal function deterioration as shown in this study. The in-hospital and long term mortality rate in our patients with left ventricular dysfunction were significantly increased confirming an earlier study by Appoo et al with a follow-up of 5 years.[9] Hazard ratio's for death In Appoo's study were adjusted for several known independent variables except postoperative renal dysfunction. The data from our study however, demonstrate an important contribution of postoperative renal dysfunction on long term mortality, and in patients with preoperative left dysfunction the mortality risk almost doubled.
In the present study we focused on the effects of preoperative left ventricular dysfunction and early postoperative renal dysfunction on long-term mortality. In addition we identified other independent risk factors associated with adverse outcome including age, preoperative renal function and the use of venous conduits only.
A decreased survival rate due to cardiovascular risk factors has primarily been described in patients with end-stage kidney disease. However, there is increasing evidence that mild to moderate preoperative renal dysfunction is associated with adverse long-term outcome in patients with several cardiovascular disease states.[17] Shlipak et al. examined over 130.000 patients and found that established renal disase is a risk factor for death after myocardial infarction.[18] Recently Hillis et al. found that preoperative estimated glomerular filtration rate (eGFR) was an independent predictor of mortality during the follow-up after coronary artery bypass grafting.[19] Cooper et al. evaluated 500.000 patients undergoing cardiac surgery and found that operative mortality increased with declining eGFR.[20] Our study support these data because univariate and multivariate analysis revealed that preoperative renal function was significantly associated with long-term mortality.
For many years aprotinin has been used routinely to reduce perioperative blood loss in cardiac surgery. However, recently the safety of this widely used drug was questioned because of increased risk of cardiovascular events, postoperative renal dysfunction, and long-term mortality.[21,22] In our study aprotinin was used to the discretion of the surgeon in 18% of the patients. In these patients we observed an increased risk of postoperative myocardial infarction and a trend towards postoperative renal dysfunction. However, after adjusting for confounding variables in multivariate analysis we found no association with long-term mortality.
The mechanism of the adverse effects of aprotinin are not fully understood. Particularly the link between the observed postoperative organ injury and long term mortality remains unclear. One of the explanations is that aprotinin is the mediator of long term death via coronary thrombosis.[21,22] A recent alternative hypothesis is that renal injury leads to chronic kidney disease, which is an additional risk factor for cardiovascular

morbidity and mortality.[23] Postoperative renal dysfunction after cardiac surgery is multifactorial in origin and aprotinin is clearly one of the factors involved. The data of our study, demonstrating worse outcome after renal injury, supports this hypothesis. Additional prospective follow up studies, using a sensitive definition of postoperative renal dysfunction, might address this clinically important issue.

This study has some limitations. First, this study is a single-center experience and may not be generalizable to other medical centers. Differences in selection and patient treatment may to some extent influence outcome. However, risk factors for postoperative renal function deterioration are consistent with the risk factors found in previous studies, and the in-hospital and long-term mortality are in line with the results of other studies. Second, multivariate analysis has been used to reduce confounding in determining the long-term mortality risk with several variables. However, additional confounders could have influenced our results; differences in additional medical therapy with antiplatelet drugs, management of dyslipidimias, or ACE inhibition in this population could have influenced outcome.

In conclusion postoperative renal function deterioration and preoperative left ventricular dysfunction both independently identify largely non-overlapping groups of patients with increased long-term mortality following CABG surgery. From a clinical perspective it is important that, in patients with both risk factors the long-term mortality nearly doubled. Thus, these risk factors identify patients who may benefit from more prolonged and intensive medical follow up, and treatment strategies.

## References


1. Bhat JG, Gluck MC, Lowenstein J, Baldwin DS. Renal failure after open heart surgery. *Ann Intern Med* 1976; 84: 677-682
2. Brown JR, Cochran RP, Dacey LJ, Ross CS, Kunzelman KS, Dunton RF, Braxton JH, Charlesworth DC, Clough RA, Helm RE, Leavitt BJ, Mackenzie TA, O'Connor GT. Peroperative increases in serum creatinine are predictive of increased 90-day mortality after coronary artery bypass graft surgery. *Circulation* 2006; 114[suppl 1]:1-409-1-413.
3. Loef BG, Epema AH, Smilde TD, Henning RH, Ebels T, Navis G, Stegeman CA. Immediate postoperative renal function deterioration in cardiac surgical patients predicts in-hospital mortality and long-term survival. *J Am Soc Nephrol* 2005; 16: 195-200
4. Beattie WS, Karkouti K. Con: Aprotinin has a good efficacy and safety profile relative to other alternatives for prevention of bleeding in cardiac surgery. *Anesth Analg* 2006; 103:1360-4
5. Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT**.** Renal dysfunction after myocardial revascularization: Risk factors, adverse outcomes, and hospital resource utilization. *Ann Intern Med* 1998; 128: 194-203
6. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005; 16: 3365-70
7. Welten GMJM, Schouten O, Chondrol M, Hoeks SE, Feringa HH, Bax JJ, Dunkelgrün M, van Gestel YR, van Domburg RT, Poldermans D. Temporary worsening of renal function after aortic surgery is associated with higher long-term mortality. *Am J Kidney Dis* 2007; 50: 219-228
8. Chertow GM, Lazarus JM, Christiansen CDL, Cook EF, Hammermeister KE, Grover F, Daley J. Preoperative renal risk stratification. *Circulation* 1997; 95: 878-84
9. Appoo J, Norris C, Merali S, Graham MM, Koshal A, Knudtson ML, Ghali WA. Long-term outcome of

isolated coronary artery bypass surgery in patients with severe left ventricular dysfunction. *Circulation* 2004; 110[suppl II]: II-13-II-17

10. Shapira OM, Hunter CT, Anter E, Bao Y, DeAndrade K, Lazar HL, Shemin RJ. Coronary artery bypass grafting in patients with severe left ventricular dysfunction-early and mid-term outcomes. *J Card Surg* 2006; 21: 225-232
11. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16 : 31-41
12. Ryckwaert F, Boccara G, Frappier JM, Colson PH. Incidence, risk factors, and prognosis of a moderate increase in plasma creatinine early after cardiac surgery. *Crit Care Med* 2002; 30: 1495-98
13. Varnauskas E. Twelve-year follow-up of survival in the randomized European Coronary Surgery Study. *N Engl J Med* 1988; 319: 332-7
14. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, Hiesmayr M. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. *J Am Soc Nephrol* 2004; 15: 1597-605
15. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. A cohort analysis *JAMA* 1996; 275:1489-1494
16. Brown JR, Cochran RP, Dacey LJ, Ross CS, Kunzelman KS, Dunton RF, Braxton JH, Charlesworth DC, Clough RA, Helm RE, Leavitt BJ, Mackenzie TA, O'Connor GT. Perioperative increases in serum creatinine are predictive of increased 90-day mortality after coronary artery bypass surgery. *Circulation* 2006; 114[suppl 1]:1-409-1-413.
17. Best PJ, Lennon R, Ting HH, Bell MR, Rihal CS, Holmes DR, Berger PB**.** The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol* 2002; 39: 1113-19
18. Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med* 2002; 137: 555-62
19. Hillis GS, Croal BL, Buchan KG, El-Shafei H, Gibson G, Jeffrey RR, Millar CG, Prescott GJ, Cuthbertson BH. Renal function and outcome from coronary bypass grafting: Impact on mortality after 2.3-year follow-up. *Circulation* 2006; 113: 1056-62
20. Cooper WA, O´Brien SM, Thourani VH, Guyton RA, Bridges CR, Szczech LA, Petersen R, Peterson ED. Impact of renal dysfunction on outcomes of coronary artery bypass surgery: results from the Society of Thoracic Surgeon´s National Adult Cardiac Database. *Circulation* 2006; 113: 1063-70
21. Mangano DT, Tudor IC, Dietzel C. Investigators of the multicenter study of the perioperative ischemia research group; ischemia research and education foundation. The risk associated with aprotinin in cardiac surgery. *N Eng J Med* 2006; 354:353-65
22. Mangano DT, Miao Y, Vuylsteke A, Tudor IC, Juneja R, Filipescu D, Hoeft A, Fontes ML, Hillel Z, Ott E, Titov T, Dietzel C, Levin J. Investigators of the multicenter study of the perioperative ischemia research group; ischemia research and education foundation. Mortality associated with aprotinin during 5 years following coronary artery bypass surgery. *JAMA* 2007; 297: 471-79
23. Coca SG, Parikh CR. Long-term mortality associated with aprotinin following coronary artery bypass graft surgery. *JAMA* 2007; 297: 2475-6